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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/828,505	Applicant(s) RAZ ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5,7,10,14,20,21,23-25 and 27-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *27-32* is/are allowed.

6)☒ Claim(s) *2,4,7,10,14,20,21,23 and 33* is/are rejected.

7)☒ Claim(s) *3,5,24 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed on May 05, 2003 in Paper No. 13 has been entered.

Amended claims 2-5, 7, 10, 14, 20-21, 23-25 and 27-33 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Response to Amendment

The art rejections of record are withdrawn in light of Applicants' amendment.

Upon reconsideration, following is a new ground of rejection.

Claim Rejections - 35 USC § 112

Amended claims 10, 14, 20-21 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing a Th2 immune response to a plant allergen, said method comprises a co-administering to a mammal an effective amount of a polynucleotide of claim 2 and an effective amount of an immunostimulatory nucleotide sequence (ISS) comprising an unmethylated 5'-CG-3" nucleotide sequence to reduce a Th2 immune response to the allergen, does not reasonably provide enablement for a method for reducing a Th2 immune response to a plant allegen in <u>any subject</u> or <u>without the co-administration</u> of an effective amount of the polynucleotide composition of claim 2 and an effective amount the ISS in any

subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Amended claims 10, 14, 20-21 and 33 are drawn to a method for reducing a Th2 immune response to a plant allergen comprising administering to a subject an effective amount of a polynucleotide composition of claim 2 and an effective amount of an immunostimulatory nucleotide sequence (ISS) comprising an unmethylated 5'-CG-3" nucleotide sequence to reduce a Th2 immune response to the allergen.

The instant specification is not enabled for such a broadly claimed invention for the reasons discussed below.

(a) The breadth of the claims. The claims encompass a method for reducing a Th2 immune response to a plant allergen in any subject including any vertebrate such as a fish, a frog as well as a mammal (see instant specification, page 11, paragraph 0042). Additionally, the claimed method does not require co-administration of an effective amount of the polynucleotide composition of the present invention and an effective amount of the immunostimulatory nucleotide sequence.

(b) The state of the art. At the effective filing date of the present application, little was known on the immune responses in vertebrate species such as a fish or a frog, let alone on the specific suppression of a Th2 immune response to a plant allergen, and more specifically a reduction in the level of IgE specific for the plant allergen in a fish or a frog as encompassed by the instant claims using an effective amount of the polynucleotide composition and the ISS of the present invention. Additionally, Caufield (WO 98/52962) clearly teaches the lack of an adjuvant effect in a situation where a CpG containing oligonucleotide is injected in the opposite leg from the antigen injected site (see example 5 on pages 25-26).

(c) The amount of direction or guidance presented. Apart from the exemplification showing that upon co-administration of the immunostimulatory sequence of SEQ ID NO:1 containing the AACGTT motif with the plasmid pNDKm/hssHAΔ36Amb a1 encoding a ragweed allergen into mice that were sensitized to Amb a1, a significant reduction of Amb a1-specific IgE was obtained at week 8 following subsequent challenges (example 6), the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain a similar reduced Amb a1-specific IgE and/or a shift in the immune response in any subject including a fish or a frog or wherein the immunostimulatory sequence is not co-administered together with the polynucleotide encoding a plant allergen of the present invention. An extensive search for the prior art at the effective filing date of the present application revealed that little has been known on the immune systems of vertebrate species such as a fish or a frog, let alone on the specific suppression of a Th2 immune response to a plant allergen, and more

specifically a reduction in the level of IgE specific for the plant allergen in a fish or a frog as encompassed by the methods as claimed. Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As such, the desired end-results contemplated by Applicants for a broad number of vertebrate species encompassed the method as claimed would not be predictive. The instant specification also fails to provide sufficient guidance for a skilled artisan on how to attain the desired results (e.g., a reduction of a Th2 immune response, specifically a reduction in the level of IgE specific to a plant allergen) in any subject without the co-administration of an effective amount of the polynucleotide composition and an effective amount of the ISS of the present invention. In light of the teachings of Caufield as noted previously, it is unclear from this disclosure whether the administration of the polynucleotide and the ISS of the present invention at different sites would also result in the desired reduction of a Th2 immune response or a reduction in the level of IgE specific for the plant allergen. Since the prior art at the effective filing date of the present application as discussed above does not provide such guidance, it is incumbent upon the present application to do so. Otherwise, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed methods.

(d) The unpredictability of the art. The physiological art is recognized as unpredictable (MPEP 2164.03), let alone for the specific suppression of a Th2 immune response to a plant allergen, or more specifically for reducing the level of IgE specific for a plant allergen in any vertebrate including a fish or a frog as encompassed by the methods as claimed. Furthermore, with respect to DNA vaccines containing the CpG

motif McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999; IDS) have noted that the route of administration and DNA doses as well as other factors such as the antigen, the dose of antigen, the co-expression of cytokines, and whether other adjuvant is used are also involved in determining the types of host immune responses elicited (page 313, see the section titled "Role of CpG immunostimulatory sequences). As such, with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for one skilled in the art to make and use the full scope of the methods as claimed.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the physiological art, particularly the genetic immunization art for allergy treatment, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Examiner notes that Applicants have not presented any argument in the amendment filed on May 05, 2003 in Paper No. 13 regarding to the issue of co-

administration of the polynucleotide composition and the ISS set forth in the previous Office Action.

Claim Rejections - 35 USC § 102

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Singh et al. (U.S. Patent No 5,965,455) as evidenced by Schultz et al. (Gene 54:113-123, 1987).

Singh et al. disclose nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments (do not contain native signal sequence) of the nucleic acid sequences coding for parts of Lol pIb that elicit an immune response in mammals such as the stimulation of minimal amounts of IgE, binding of IgE, eliciting the production of IgG and IgM antibodies (see abstract and col. 9, lines 6-10). Singh et al. further provide expression vectors comprising these nucleic acid sequences coding for at least one Lol p Ib ryegrass pollen allergen or at least one antigenic fragment thereof in cultured host cells, including mammalian host cells as well as yeast cells (see col. 11, lines 1-20). It is also noted that Sigh et al. teach that the expressed Lol p Ib proteins and fragments or peptides can be purified from host cells as well as from the cell culture medium (col. 12, lines 6-8). Singh et al. specifically teach suitable vectors for expression in yeast cells include the vector taught by Schultz et al. disclosed in Gene 54:113-123, 1987(col. 11, lines 18-21). The yeast expression vector (pYEBVC-1) utilized by Schultz for expressing a 400-kDa envelope glycoprotein into the culture fluids of JRY188 transformants contain a yeast MFα1 promoter and pre-pro-leader polypeptide (page 115, col. 1, top of last paragraph).

Accordingly, the teachings of Singh et al. meet all the limitation of the instant claim as evidenced by Schulz et al. Therefore, Singh et al. anticipate the instant claim.

Claim Rejections - 35 USC § 103

Claims 2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (U.S. Patent No 5,965,455) as evidenced by Schultz et al. (Gene 54:113-123, 1987) and in view of Kim et al. (Gene 199: 293-301, 1997; IDS).

Singh et al. disclose nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments (do not contain native signal sequence) of the nucleic acid sequences coding for parts of Lol pIb that elicit an immune response in mammals such as the stimulation of minimal amounts of IgE, binding of IgE, eliciting the production of IgG and IgM antibodies (see abstract and col. 9, lines 6-10). Singh et al. further provide expression vectors comprising these nucleic acid sequences coding for at least one Lol p Ib ryegrass pollen allergen or at least one antigenic fragment thereof in cultured host cells, including mammalian host cells as well as yeast cells (see col. 11, lines 1-20). It is also noted that Sigh et al. teach that the expressed Lol p Ib proteins and fragments or peptides can be purified from host cells as well as from the cell culture medium (col. 12, lines 6-8). Singh et al. specifically teach suitable vectors for expression in yeast cells include the vector taught by Schultz et al. disclosed in Gene 54:113-123, 1987(col. 11, lines 18-21). The yeast expression vector (pYEBVC-1) utilized by Schultz for expressing a 400-kDa envelope glycoprotein into the

culture fluids of JRY188 transformants contain a yeast MFα1 promoter and pre-pro-leader polypeptide (page 115, col. 1, top of last paragraph).

Singh et al. do not specifically teach the preparation of nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and their peptide fragments, wherein at least one codon of the nucleic acid sequences encoding the allergic antigens is modified to an analogous codon of a host species.

At the effective filing date of the present application, Kim et al. already teach that the choice of synonymous codons in many species is strongly biased and that a correlation exists between high expression and the use of selective codons in a given organism (page 294, col. 1, first sentence of second paragraph). Additionally, Kim et al. disclose non-random codon-usage patterns in highly expressed human and yeast genes (Figure 1).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the nucleic acid sequences encoding ryegrass pollen allergen Lol p Ib family members of Singh et al. by substituting codon bases of these nucleic acid sequences with analogous codon bases commonly used in a given selected expression host cell (e.g., mammalian cells or yeast cells) in order to increase expression efficiency.

One of ordinary skilled artisan would have been motivated to carry out the above modification in order to obtain an efficient and high level of expression of recombinant ryegrass pollen allergens in any given host cells, for example in yeast cells, in light of the teachings of Kim et al.

The modified nucleic acids as a result of the combined teachings of Singh et al., Schultz et al. (Gene 54:113-123, 1987), and Kim et al. are indistinguishable from the polynucleotide composition of the instantly claimed invention. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 7 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rogers et al. (U.S. 5,776,761) in view of Singh et al. (U.S. Patent No 5,965,455) and Schultz et al. (Gene 54:113-123, 1987).

Rogers et al. already disclose cDNAs encoding Amb al allergic proteins or peptides (do not contain native signal peptide) from ragweed, and teach techniques to clone as well as produce the allergic protein or peptide in cultured transforming host cells (see abstract, col. 19, lines 36-52).

Rogers et al. do not specifically teach to the preparation of nucleic acid sequences coding for Amb a1 allergic proteins or peptides, and wherein such nucleic acids contain a heterologous signal sequence.

However, at the effective filing date of the present application, Singh et al. already disclose nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments (do not contain native signal sequence) of the nucleic acid sequences coding for parts of Lol pIb that elicit an immune response in mammals such as the stimulation of minimal amounts of IgE, binding of IgE, eliciting the production of IgG and IgM antibodies (see abstract and col. 9, lines 6-10). Specifically,

Sigh et al. teach that the expressed Lol p Ib proteins and fragments or peptides can be expressed and purified from host cells (mammalian and yeast cells) as well as from the cell culture medium (col. 12, lines 6-8). Singh et al. specifically teach suitable vectors for expression in yeast cells including and not limited to the vector taught by Schultz et al. disclosed in Gene 54:113-123, 1987(col. 11, lines 18-21). The yeast expression vector (pYEBVC-1) utilized by Schultz for expressing a 400-kDa envelope glycoprotein into the culture fluids of JRY188 transformants contain a yeast MFα1 promoter and pre-pro-leader polypeptide (page 115, col. 1, top of last paragraph). Schulz et al. further teach that the *S. cerevisiae* yeast system has been used for the expression, in biologically active form, of medically significant proteins such as vaccines and therapeutic agents. In particularly, the signals for the post-translational addition of core oligosaccharides are similar in yeast and eukaryotic cells, and heterologous proteins are specifically N- or O-glycosylated (page 114, bottom of col. 1).

Accordingly, it would have been obvious for an ordinary skilled artisan to clone and express the nucleic acid sequences encoding Amb al allergic proteins or peptides of Rogers et al. in a yeast expression system taught by Singh et al and Schulz for the preparation of Amb a1 allergic proteins or peptides to desensitize an individual in need of treatment as contemplated by Rogers et al.

One of ordinary skilled artisan would have been motivated to carry out the above modification because the *S. cerevisiae* yeast system has been used for the expression, in biologically active form, of medically significant proteins such as vaccines and

therapeutic agents as taught by Schultz, and that the same system has been taught by Singh et al. to express rye grass pollen allergens.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

Claims 27-32 are allowed.

Claims 3, 5 and 24-25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

Gerald D. Leffers Jr.
PATENT EXAMINER
A.U. 1636